(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 July 2001 (12.07.2001)

PCT

(10) International Publication Number
WO 01/49638 A2

(51) International Patent Classification[7]: C07C

(21) International Application Number: PCT/IN01/00001

(22) International Filing Date: 1 January 2001 (01.01.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
12/MUM/2000 4 January 2000 (04.01.2000) IN

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/49638 A2

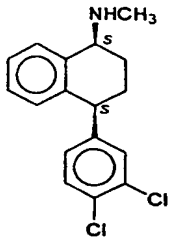
(54) Title: A PROCESS FOR CONVERTING STEREOISOMERS OF SERTRALINE INTO SERTRALINE

(57) Abstract: A process for converting the cis (1R, 4R), trans (1S, 4R), and trans (1R, 4S) stereoisomers of sertraline into sertraline comprises, providing an initial reaction mixture which contains at least one of these stereoisomers, converting the sertraline stereoisomers into an imine form of sertraline. The imine form of sertraline is then reduced so that sertraline and at least one sertraline stereoisomer byproduct is produced in the reaction mixture. The sertraline is then recovered from the reaction mixture, e.g., by fractional crystallization (followed by resolution of sertraline from the cis (1R, 4R) stereoisomer, if necessary). The reaction mixture is then recycled through the same steps so that sertraline is produced from its stereoisomers in an asymptotic yield.

A PROCESS FOR CONVERTING STEREOISOMERS OF SERTRALINE INTO SERTRALINE

Field of invention

The present invention relates to a novel process for obtaining therapeutically effective sertraline of formula 1. More particularly, the invention relates to a process for obtaining sertraline from stereoisomers of sertraline such as (1R,4R) N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine of formula 2, hereinafter referred to as cis (1R,4R) isomer, or trans (1S,4R) isomer of formula 3 or trans (1R,4S) isomer of formula 4 or mixtures thereof (1S, 4S) N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine of formula 1, is commonly known as sertraline (INN Name).



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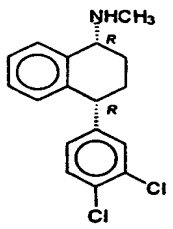

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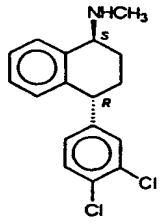

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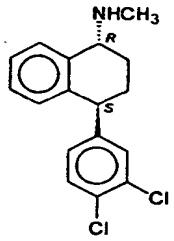

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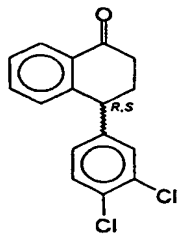
These aforesaid isomers of formula 2, 3 and 4 are undesired stereoisomers of sertraline of formula 1, and are invariably co-produced during the manufacture of this drug by known processes such as that disclosed in United States Patent No. 4,536,518, which is incorporated herein by reference. More particularly, the present invention relates to a novel process for recycling the undesired stereoisomers, both the trans (1S,4R) and (1R,4S) isomers as well as the cis (1R,4R) isomer, to obtain sertraline in asymptotic amounts through an iterative process. Sertraline hydrochloride (commonly known as Zoloft®) is an important drug useful in the treatment of depression, obsessive-compulsive disorder and panic disorder.

Background of the Invention

N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine has two chiral centres and hence has four stereoisomeric forms, namely, the (1R,4R), (1S,4S),

(1R,4S) and (1S,4R) isomeric forms. Of these, the active stereoisomer for therapeutic purpose is sertraline i.e. the cis (1S,4S) isomer of formula 1.

United States Patents No. 4,536,518 and No. 4,556,676 assigned to Pfizer, disclose a multi-step process for synthesis of pure (1S,4S) N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine from 3,4-dichlorobenzophenone. The process proceeds via racemic 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone, a compound of formula 6.



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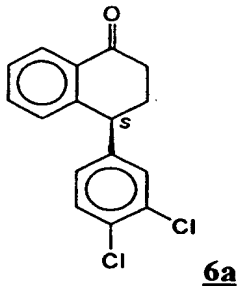
The ketone is condensed with methylamine to form a racemic imine mixture of formula 5c (shown below). The racemic imine is then reduced by means of catalytic hydrogenation or by the use of a metal hydride complex to N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine, which is a racemic mixture of the cis and trans isomers. Trans isomers are separated from the cis isomers by fractional crystallization. Resolution of the separated cis racemate with optically active precipitant acid, such as D-(-)-mandelic acid in a classical manner, finally affords the desired cis-(1S,4S)-enantiomer (sertraline). The process has the disadvantage that large amounts of the undesired isomers of formulas 2, 3 and 4 are co-produced thereby lowering the overall yield of sertraline and increasing the production cost.

United States Patents No. 4,777,288 and No. 4,839,104 assigned to Pfizer, disclose processes for the preparation of 4-(3,4-dichlorophenyl)-4-ketobutanoic acid in pure form and in high yield. The 4-(3,4-dichlorophenyl)-4-ketobutanoic acid is converted to racemic 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone, a compound of formula 6. Also, PCT International Publication No. WO 98/15516 discloses a process to prepare a compound of formula 6 in pure form by reacting α-naphthol and o-dichlorobenzene

wherein the amount of by-product 4-(2,3-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone is decreased below 1 %. The racemic tetralone obtained by the processes of US 4,777,288; US 4,839,104 and WO 98/15516 may be converted to sertraline by the process disclosed in US 4,536,518 and US 4,556,676. The processes thus carry with them the prior art disadvantage in that large amounts of the undesired isomers of formulas 2, 3 and 4 are co-produced thereby lowering the overall yield of sertraline and increasing the production cost.

United States Patent No. 5,196,607 assigned to Pfizer discloses a multi-step process for preparing chiral (4S)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenone of formula 6a



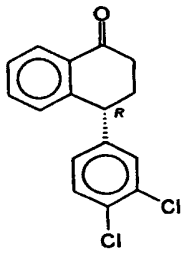
6a

in pure form and high yield with an enantiomer ratio of 79:21. However, the 4S enantiomer is converted as described in United States Patent No. 4,536,518 to a mixture of sertraline and the trans (1R,4S) isomer and then the two isomers are required to be separated by chromatographic means to ultimately yield the desired compound, sertraline. This patent does not disclose any method for recycling the undesired trans (1R,4S) stereoisomer of sertraline.

Yet another method is described in United States Patent No. 5,466,880 whereby the chiral tetralone is prepared in an elaborate five-step process starting from 4-(3,4-dichlorophenyl)-4-ketobutanoic acid. Tetrahedron, 48(47), 10239 (1992) provides another method for preparing the chiral (4S) tetralone by reduction of 4-ketobutanoic acid ester with an asymmetric carbonyl reducing agent. The preparation of chiral tetralone allows for major improvement in the overall synthesis of sertraline in that the unwanted cis (1R,4R)

isomer and trans (1S,4R) isomer are not co-produced when (4S) tetralone is converted to sertraline by methods described in United States Patent Nos. 4,536, 518; 4,556, 676; 4,777,288; and 4,839,104. The trans (1R,4S) isomer is co-produced and is separated from sertraline. However, the patents do not disclose any method for recycling the undesired stereoisomer(s) of sertraline.

PCT International Publication No. WO 95/15299 (Pfizer) describes a method for preparing chiral (4S)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenone of formula 6a by asymmetric reduction of the corresponding racemic mixture with asymmetric ketone reducing agents viz. chiral oxazaborolidine compounds to produce a mixture of cis and trans alcohols, from which the (4S) enantiomer is separated and oxidized to give the (4S) chiral tetralone.



6b

The remaining mixtures of alcohols are oxidized to produce (4R) tetralone of formula 6b, which is then isomerised to racemic mixture of formula 6, with a base and recycled. The (4S) tetralone is then converted to sertraline by methods described in United States Patent Nos. 4,536,518; 4,556,676; 4,777,288; and 4,839,104. The trans (1R,4S) stereoisomer is co-produced and is separated from sertraline. However, the patents do not disclose any method for recycling the undesired stereoisomer(s) of sertraline.

The PCT International Publication No. WO 98/27050 discloses a three step process for the preparation of a mixture of sertraline and its cis (1R,4R) isomer using a novel N-oxide intermediate. However, this patent does not disclose any method for recycling the undesired stereoisomer of sertraline.

In a recent publication (Organic Lett. 1(2), 293, 1999) an enantioselective synthesis of sertraline using an anionic imine ring closure methodology is described starting from dichlorocinnamic acid.

In all the methods described above, eventual isomer separation is inevitable. However, none of the methods discussed above provides methods for recycling the unwanted stereoisomers of sertraline. A process for recycling trans isomer of sertraline is described in United States Patent No. 5,082,970. The process involves refluxing the trans isomer or a mixture with about an equal part by weight of the corresponding cis isomer with about 2 molar equivalents of a base such as potassium tert-butoxide for 48 hours in an inert polar solvent to afford a cis-trans mixture in a ratio of about 2:1. However this method appears to have certain drawbacks in that

i) an excess of base (2 mole equivalents) is used,

ii) requires 48 hours of reflux, and most importantly,

iii) the method is not exemplified with cis isomer containing (1R) centre, which incidentally, is the major unwanted isomer that is co-produced in equal amounts along with the desired cis-(1S) isomer. An experiment performed by the inventors herein on the cis (1R,4R) isomer, under the conditions described in the above-referred patent, did not result in isomerisation at the C-1 centre. This is understandable since the hydrogen at the C-1 position in sertraline isomers is not reactive under the conditions described, and hence is not susceptible to isomerisation.

It is therefore, the object of the present invention to develop an alternate simple process whereby the unwanted isomers, both trans as well as the cis (1R,4R) isomer could be recycled to produce ultimately the cis (1S,4S) isomer in a simple manner which is commercially feasible.

Summary of the Invention

Thus the invention relates to a process for producing sertraline comprising the following steps :

I. providing in initial reaction mixture containing at least one sertraline stereoisomer, and converting said sertraline stereoisomer into an imine form of sertraline ;

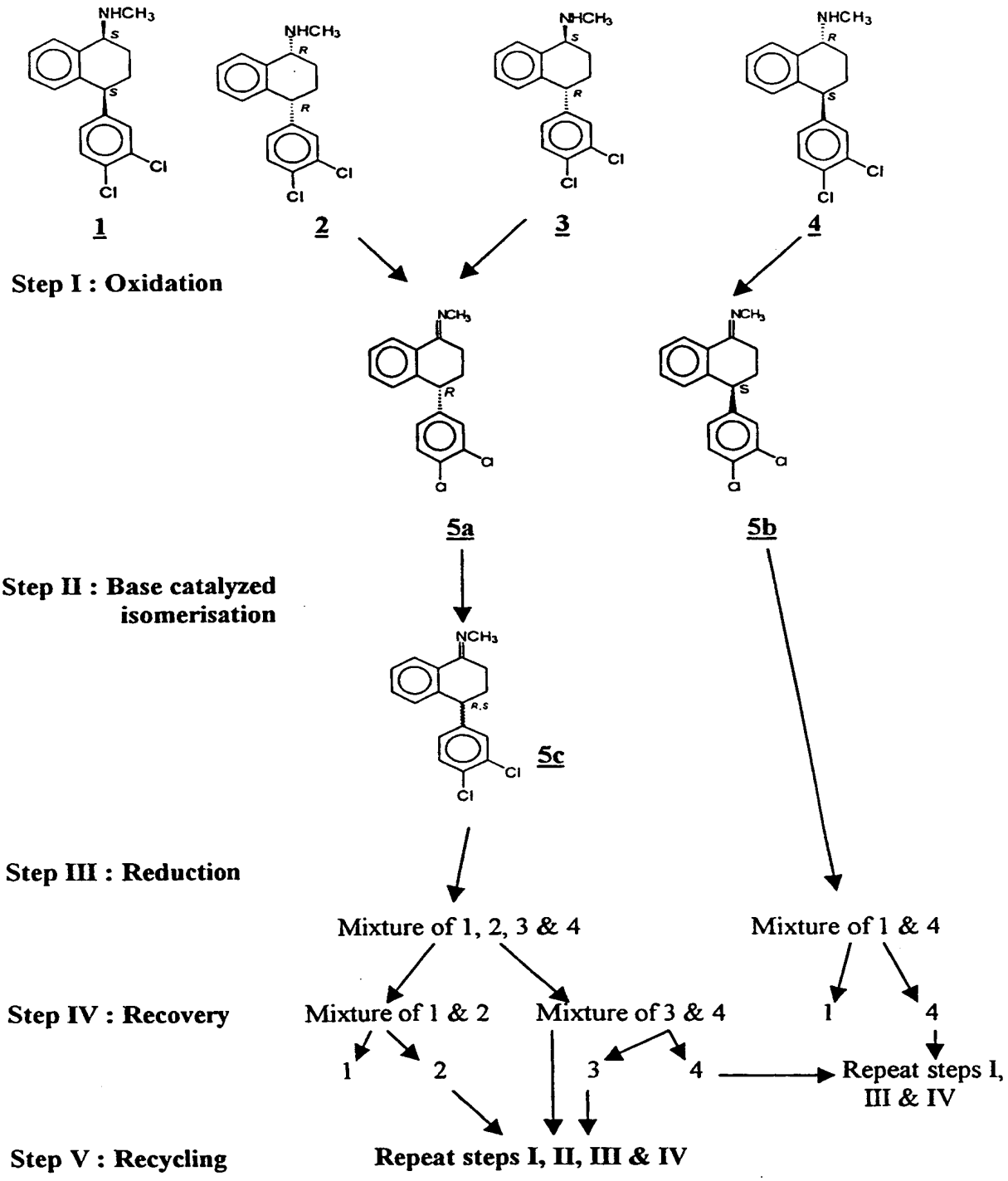
II. optional base catalyzed isomerisation of the imine form of sertraline ;

III. reducing the imine form of sertraline into sertraline and at least one stereoisomer of sertraline;

IV. recovering sertraline from the reaction mixture ; and

V. recycling the remaining isomers of sertraline into step I.

The process described herein may be illustrated in the following schematic diagram :



SCHEME I

The sertraline stereoisomer used in the process of the invention is one or more of the isomers of formula 2,3 &4. The stereoisomers are converted into imine form. The cis

(1R,4R) isomer of formula 2; trans (1S, 4R) isomer of formula 3 and mixtures thereof gets converted to the corresponding (4R)-imine of formula 5a. On the other hand trans (1R,4S) isomer of formula 4 get converted to the corresponding (4S)– imine of formula 5b. While a mixture of isomers of formulas 2 and 4, or a mixture of isomers of formulas 3 and 4, or a mixture of isomers of formula 2, 3 and 4 gets converted to the corresponding mixture of (4R)- and (4S)-imines of formula 5c. When (4R)-imine of formula 5a is produced it is subjected to base catalyzed isomerisation to produce a racemic imine mixture of (4R)- and (4S) – imines of formula 5c. The mixture of (4R)- and (4S)-imines of formula 5c is reduced to obtain a mixture of sertraline with stereoisomers of formula 2, 3 and 4. On the other hand when (4S)-imine of formula 5b is produced, the same is reduced obtained in step I to obtain a mixture of sertraline and trans (1R,4S) isomer of formula 4. Sertraline thus obtained is separated from the reaction mixture e.g. by fractional crystallization, and resolved, if necessary from the cis (1R,4R) isomer. Thereafter or simultaneously, the process is repeated in an interactive procedure so that sertraline is produced in an asymptotic yield.

The process described in this invention permits convenient recycling of the unwanted steroisomers of sertraline on a commercial scale as the entire process is simple and requires inexpensive raw materials.

The initial reaction mixture contains one or more stereoisomers of sertraline in the form of cis (1R,4R) stereoisomer (formula-2), trans (1S,4R) stereoisomer (Formula-3), and trans (1R,4S) stereoisomer (formula 4). The initial reaction mixture may be obtained from known prior art processes for producing sertraline wherein undesired stereoisomers of formula 2, 3 and 4 are co-produced. Alternatively, the initial rection mixture is the mixture remaining after separation of sertraline in Step IV of the present invention.

Detailed Description of the Invention

The present invention relates to a process whereby the undesired isomers, both trans isomers as well as the cis (1R,4R) isomer, of sertraline, are converted to the desired cis (1S,4S) isomer in a manner, which is simple, convenient, easily scaleable and

commercially feasible. The term sertraline as used herein refers to both sertraline base as well as its pharmaceutically acceptable acid addition salts.

The inventive process differs from prior art methods of producing sertraline in that it proceeds by converting unwanted stereoisomers of formula 2, 3 and 4 that are co-produced with sertraline into sertraline. The undesired stereoisomers are first converted into an imine form of sertraline which eliminates the chirality at the C-1 position. The imine formed is stable and does not hydrolyze to ketone under the conditions of the present invention. This step is quite useful in comparison to prior art methods because it obviates the need to convert a ketone into an imine (when ketone is one of the intermediates produced). Once the imine is formed, it is then necessary to isomerize the C-4 position since the (4R) components are the major unwanted stereoisomers in the starting mixture. Isomerization is achieved under base catalyzed conditions in a very facile manner, a process hitherto unreported.

According to the process of the present invention, cis (1R,4R) isomer of formula 2 and/or trans (1S,4R) isomer of formula 3, is converted to the corresponding (4R)-imine of formula 5a. The trans (1R,4S) isomer of formula 4 is converted to the corresponding (4S)-imine of formula 5b. A mixture of stereoisomers of formula 4 and any one or both of formulae 2 and 3 is converted to a mixture of (4R)- and (4S)-imines of formula 5c. The conversion may be carried out by oxidation in the presence of a base using a halogen ion generating reagent such as N-haloamides, N-haloimides and N-halohydantoins. The step of converting the stereoisomer to imine is preferably carried out by oxidation using a hypohalite. The preferred halogen ion generating reagents are N-bromosuccinimide and N-chlorosuccinimide. The hypohalite may be added to the reaction mixture or generated in-situ by reaction of a halogen with a base preferably in a protic solvent. Examples of bases that may be used include alkali metal hydroxides such as LiOH, NaOH, KOH, CsOH; and alkali metal carbonates such as Li_2CO_3, Na_2CO_3, K_2CO_3. The preferable bases that can be employed are alkali metal hydroxides such as LiOH, NaOH, KOH, CsOH. The most preferred is NaOH. The protic solvents that may be used include aqueous or alcoholic solvent(s) or mixtures thereof. The more preferred solvent is methanol.

According to the process of the present invention the (4R)-imine of formula 5a, when processed, is subjected to base catalysed isomerisation to yield a racemic imine mixture of formula 5c. Base catalyzed isomerisation may be carried out by using non-nucleophilic organic bases. Examples of non-nucleophilic organic bases that may be used include metal alkoxides, metal amides, dimsyl or trityl metal salts; and the like. Preferably the non-nucleophilic organic base is a metal alkoxide; more preferably an alkali metal alkoxide; most preferably potassium tert-butoxide. Preferably, the alkali metal alkoxide may be used in a mole ratio of about 5% to about 20%, preferably 10% with respect to the imine. The solvent for the isomerisation reaction is an aprotic solvent that may include ethers, acyclic or cyclic, such as diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, 1,4-dioxane, and the like; aromatic hydrocarbons such as toluene, xylenes, and the like. The preferred solvents are ethers such as tetrahydrofuran and 1,4-dioxane. The most preferred solvent is tetrahydrofuran. The temperature for the isomerisation reaction may range from ambient to about 140° C, preferably about 70 ° C to about 75° C. The reaction time ranges from 1 to 10 hours, preferably about 2 to about 3 hours. After the reaction is completed, the reaction mixture is concentrated and degassed, an appropriate quantity of water is added and the isomerised racemic imine is isolated by filtration. In the case where the solvent used for the reaction is immiscible with water, the reaction mixture is simply washed with an appropriate quantity of water, and solvent is degassed to recover the isomerised racemic imine.

The reduction of the mixture of (4R)- and (4S)-imines of formula 5c is carried out to obtain a mixture of sertraline with stereoisomers of formulas 2, 3 and 4; or reduction of (4S)-imine of formula 5b is carried out to obtain a mixture of sertraline and trans (1R,4S) isomer of formula 4. Reduction may be achieved by the use of a metal hydride complex or by means of catalytic hydrogenation. Preferably, the mixture of (4R)- and (4S)-imine of formula 5c or the (4S)-imine of formula 5b is reduced by catalytic hydrogenation. Catalytic hydrogenation results in a mixture of stereoisomers wherein the cis isomer(s) are present in amounts greater than the trans isomer(s). More preferably, the imine(s) is/are catalytically hydrogenated to get predominantly the cis isomers, along with minor quantity of trans isomers. The catalytic hydrogenation is preferably carried out in protic solvents such as primary, secondary, tertiary alcohols or mixtures thereof. Examples of the

hydrogenation catalysts that may be used include Raney Nickel or precious metal promoters such as platinum, palladium on supports such as carbon, graphite, calcium carbonate, and the like. The catalytic hydrogenation may also be carried out using copper containing catalysts such as copper chromite in aprotic solvents, particularly ethers such as tetrahydrofuran.

Separation of the cis and trans isomers and subsequent resolution of cis (1R,4R) and (1S,4S) stereoisomers, or of trans (1R,4S) and (1S,4R) stereoisomers as their hydrochlorides, is carried out by methods well known to those skilled in the art and heretofore described in the literature, e.g. cis isomers may be separated from a mixture of cis and trans isomers by fractional crystallization or chromatography; and resolution of the cis (1S,4S) and cis (1R,4R) isomers may be achieved by treating a solution of cis-racemate free base with an optically active precipitant acid such as D-(-)-mandelic acid and precipitating the less soluble diastereomeric salt. Although not normally carried out it would be possible for any person skilled in the art to resolve a mixture of trans isomers of formulas 3 and 4 as described in United States No. 4,556,676.

The recycling of the undesired isomers of sertraline in the present invention is carried out as follows:

a. isolating a mixture of sertraline and cis (1R,4R) isomer from the mixture of sertraline with stereoisomers of formulas 2, 3 and 4 and if desired, repeating steps I, II, III and IV of the process of the invention. In the case mixture of trans (1R,4S) and trans (1S,4R) isomers, steps I, II, III and IV are repeated. When a mixture of sertraline and trans(1R,4S) of formula 4 is obtained in step 3 sertraline is isolated from the mixture of sertraline and trans (1R,4S) isomer of formula 4 and trans (1R,4S) isomer is thereafter, if desired, subjected to the treatment of steps I, III and IV ;

b. resolving the mixture of sertraline and cis (1R,4R) isomer of formula 2 obtained in step a; followed optionally by recycling the cis (1R,4R) isomer by repetition of steps I, II, III and IV of the process ; and

c. resolving the mixture of trans (1R,4S) and trans (1S,4R) isomers obtained in step a ; followed optionally by subjecting the trans (1S,4R) isomer to steps I, II, III and IV of the process and the trans (1R,4S) isomer to steps I, III and IV of the process.

The process described in this invention, thus permits convenient recycling of the unwanted steroisomers of sertraline to the desired (1S,4S) sertraline in asymptotic amounts through iteration. The process described is feasible on a commercial scale in view of the fact that operations involved are simple and the raw materials required are not expensive.

The invention is illustrated but not restricted by the description in the following examples.

Examples

Example 1

Preparation of (R)-N-[4-(3,4-dichlorophenyl)-3,4-dihyro-1-(2H)-naphthalenylidene]methanamine (formula 5a) from (1R,4R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine (formula 2) illustrating steps I and V of the process

(1R,4R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine 100 g (0.326 mol.) was dissolved in 900 ml methanol and 78.4g (1.96 mol.) NaOH was added to it and cooled to 30-35^0 C. To the cooled solution was added 18.5 ml (0.358 mol.) bromine during 2 hour under stirring while maintaining temperature in the range of 35-40^{0}C using an ice water bath. After stirring for 30 minutes at 30-35^{0}C, the solid formed was separated by filtration and washed with 2 x 100ml methanol. The product was then suspended in 500 ml water, stirred for 15 minutes at 25 - 30^0 C and filtered. The product was washed with 2 x 250 ml water and allowed to suck dry. The product was finally dried at 55-60^0 C under vacuum, yield 78.7 g (78.18 %, $[\alpha]_D^{25}$ (1% in chloroform) ranges from = -72° to -76°)

Example 2

Preparation of (R)-N-[4-(3,4-dichlorophenyl)-3,4-dihyro-1-(2H)-naphthalenylidene]methanamine (formula 5a) from (1R,4R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine (formula 2) hydrochloride illustrating steps I and V of the process

The procedure described in example 1 was repeated using (1R,4R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride, 10 g (0.029 mol.), except that sodium hydroxide was taken in the mole ratio 7:1 instead of 6:1 with respect to the amino compound, i.e 8.17g (0.204 mol.). The product was isolated in the same manner as in Example 1.

Example 3

Base catalyzed isomerisation of (R)-N-[4-(3,4-dichlorophenyl)-3,4-dihyro-1-(2H)-naphthalenylidene]methanamine (formula 5a) illustrating step II of the process

A suspension of 100g (0.329 mol.) (R)-N-[4-(3,4-dichlorophenyl)-3,4-dihyro-1-(2H)-naphthalenylidene]methanamine and 3.7g (0.0329 mol.) potassium tertiary butoxide in 300 ml tetrahydrofuran was heated to 70-72^0 C and stirred for 2 hours. A sample (2 ml) of the reaction mixture was withdrawn for checking specific rotation. If specific rotation was 0 ± 2°, the solvent was distilled out at atmospheric pressure and the mixture cooled to 30-35^0 C. Water 500 ml was added to the residual material and stirred for 15 min. The product was filtered, washed successively with 3 × 100 ml water and 2 × 100 ml isopropyl ether and sucked dry. The product was finally dried at 55-60^0 C under vacuum, yield was 83g (83 %).

Example 4

Preparation of racemic (R),(S)-N-[4-(3,4-dichlorophenyl)-3,4-dihyro-1-(2H)-naphthalenylidene]methanamine (formula 5c) from racemic mixture containing (1S,4R) N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine and (1R,4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine (formulas 3 and 4) illustrating steps I, II and V of the process.

The same procedure as in Example-1 was followed using racemic mixture containing (1R,4S), (1S,4R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine, 25g (0.082 mol.). The product obtained was identical to that obtained in Example 3.

Example 5

Preparation of racemic (R),(S)-N-[4-(3,4-dichlorophenyl)-3,4-dihyro-1-(2H)-naphthalenylidene]methanamine (formula 5c) from racemic mixture containing (1S,4R) N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine and (1R, 4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine (formulas 3 and 4)hydrochlorides illustrating steps I, II and V of the process.

The same procedure as in Example-2 was followed using a racemic mixture containing (1R,4S) N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride (1S,4R) N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride, 28g (0.082 mol.). The product obtained was identical to that obtained in Example-3.

Example 6

Conversion of the mixture of (R)&(S)-N-[4-(3,4-dichlorophenyl)-3,4-dihyro-1-(2H)-naphthalenylidene]methanamines (formula 5c) to (1R,4R) N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride (formula 2) and sertraline hydrochloride (formula 1) mixture illustrating steps III and IV of the process.

The isomerised imine from Example-5 83g was taken in 400 ml 2-propanol, 4.0 g of Raney-Nickel was added and hydrogenated at a pressure of 4.5-5.0 kg/cm^2 and 70-80^0 C until there was no further consumption of hydrogen. The reaction mass was filtered and the catalyst washed with 200 ml 2-propanol. From combined filtrate and washings, 200 ml of 2-propanol was distilled out at 55-60^0 C under reduced pressure and to the concentrate was added 36.5 ml (0.44 mol.) of conc. HCl. The mixture was stirred for 2 hrs at 30-35^0 C and filtered. The separated solid was washed with 200 ml of 2-propanol. The product was

then stirred with 400 ml methylene chloride, filtered, washed with 200 ml methylene chloride and then dried at 60-65^0 C to yield (1R,4R) & (1S, 4S)-sertraline hydrochlorides. The yield was 61g (68.72 %).

While the invention has been described by reference to specific embodiments, this was for purposes of illustration only and should not be construed to limit the spirit or the scope of the invention.

CLAIMS

1. A process for producing sertraline comprising the following steps :

I. providing in initial reaction mixture containing at least one sertraline stereoisomer, and converting said sertraline stereoisomer into an imine form of sertraline ;

II. optional base catalyzed isomerisation of the imine form of sertraline ;

III. reducing the imine form of sertraline into sertraline and at least one stereoisomer of sertraline;

IV. recovering sertraline from the reaction mixture ; and

V. recycling the remaining isomers of sertraline into step I.

2. The process according to claim 1, wherein said sertraline stereoisomer is selected from the group consisting of cis (1R,4R), trans (1S,4R) and trans (1R,4S) stereoisomers of sertraline and mixtures thereof.

3. The process according to claim 1 wherein said imine form of sertraline is selected from the group consisting of (4R)-imine and (4S)-imine forms of sertraline, and mixtures thereof.

4. The process according to claim 1, wherein the initial reaction mixture contains one or both of cis (1R,4R) or trans (1S,4R) stereoisomers of sertraline, are converted to (4R)-imine form of sertraline, which is then subjected to base catalyzed isomerization into a racemic mixture of (4R)- and (4S)-imine forms of sertraline.

5. The process according to claim 1, wherein said imine form of sertraline comprises a racemic mixture of (4R)- and (4S)-imine forms of sertraline, which is reduced to a mixture of sertraline, cis (1R,4R) sertraline, trans (1S,4R) sertraline, and trans (1R,4S) sertraline.

6. The process according to claim 1, wherein said initial reaction mixture contains trans (1R,4S) stereoisomer of sertraline which is converted into (4S)-imine form of sertraline.

7. The process according to claim 1, wherein said imine form of sertraline comprises (4S)-imine form of sertraline which is reduced to a mixture of sertraline and trans (1R,4S) stereoisomer of sertraline.

8. The process according to claim 1, wherein said stereoisomer of sertraline in said initial reaction mixture is converted into said imine form of sertraline by oxidation with a hypohalite.

9. The process according to claim 8, wherein said hypohalite is generated in situ in said reaction mixture by the reaction of a halogen with a base.

10. The process according to claim 9,wherein said halogen is bromine or chlorine, said base is an alkali metal hydroxide or an alkali metal carbonate, which are reacted together in a protic solvent.

11. The process according to claim 10, wherein said protic solvent is water, an alcohol, or mixtures thereof.

12. The process according to claim 11, wherein said protic solvent is methanol.

13. The process according to claim 10, wherein said alkali metal hydroxide is LiOH, NaOH, KOH, or CsOH.

14. The process according to claim 10, wherein said alkali metal carbonate is Li_2CO_3, Na_2CO_3 or K_2CO_3.

15. The process according to claim 1, wherein said stereoisomer of sertraline in said initial reaction mixture is converted to said imine form of sertraline by oxidation with a halogen ion generating reagent.

16. The process according to cliam 15,wherein said halogen ion generating reagent is N-haloamide, N-haloimide, or N-halohydantoin.

17. The process according to claim 16, wherein said halogen ion generating reagent is N-bromosuccinimide or N-chlorosuccinimide.

18. The process according to claim 1, wherein said initial reaction mixture contains one or both of cis (1R,4R) trans (1S,4R) stereoisomers of sertraline, which are converted to (4R)-imine form of sertraline, which is then subjected to base catalyzed isomerisation to produce a racemic mixture of (4R)- and (4S)-imine form of sertraline, wherein the base catalyzed isomerisation of the (4R)-imine form of sertraline is carried out using a non-nucleophilic organic base in an ether or an aromatic hydrocarbon solvent at a temperature from about ambient to about 140° C.

19. The process according to claim 18, wherein said non-nucleophilic organic base is a metal alkoxide, metal amide, or a dimsyl or trityl metal salt.

20. The process according to claim 19, wherein said non-nucleophilic base used is an alkali metal alkoxide.

21. The process according to claim 20, wherein the alkali metal alkoxide is potassium tert-butoxide.

22. The process according to claim 21, wherein the amount of alkali metal alkoxide comprises about 5 mole% to about 20 mole% of the imine form of sertraline.

23. The process according to claim 18, wherein said base is an alkali metal alkoxide and said solvent is tetrahydrofuran or 1,4-dioxane.

24. The process according to claim 23, wherein said base is potassium tert-butoxide and said solvent is tetrahydrofuran.

25. The process according to claim 24, wherein the potassium tert-butoxide is present in a mole ratio of about 5% to about 20% with respect to the imine form of sertraline.

26. The process according to claim 25, wherein the base catalysed isomerisation is carried out at a temperature in the range of about 70 ° C to about 75° C.

27. The process according to claim 1, wherein the imine form of sertraline comprises a racemic mixture of (4R)- and (4S)-imine forms of sertraline which is reduced by catalytic hydrogenation to obtain a mixture of sertraline, cis (1R,4R), trans (1S,4R), and trans (1R,4S) stereoisomers of sertraline.

28. The process according to claim 27, wherein the catalytic hydrogenation is carried out in a protic solvent.

29. The process according to claim 28, wherein said protic solvent is a primary, secondary or tertiary alcohol, or mixtures thereof.

30. The process according to claim 29, wherein the solvent is 2-propanol and the catalytic hydrogenation is carried out in the presence of Raney Nickel.

31. The process according to claim 1, wherein the mixture of sertraline and cis (1R,4R) is recovered from said reaction mixture by fractional crystallization.

32. The process according to claim 31, wherein the sertraline is recovered from said reaction mixture along with the cis (1R,4R) stereoisomer, the process further comprising isolating the sertraline from the cis (1R,4R) stereoisomer of sertraline.

33. Sertraline prepared according to the process of any of claims 1 to 32.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 July 2001 (12.07.2001)

PCT

(10) International Publication Number
WO 01/49638 A3

(51) International Patent Classification[7]: C07C 209/88, 209/52, 211/42, C07B 57/00

(21) International Application Number: PCT/IN01/00001

(22) International Filing Date: 1 January 2001 (01.01.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
12/MUM/2000 4 January 2000 (04.01.2000) IN

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
6 December 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/49638 A3

(54) Title: A PROCESS FOR CONVERTING STEREOISOMERS OF SERTRALINE INTO SERTRALINE

(57) Abstract: A process for converting the cis (1R, 4R), trans (1S, 4R), and trans (1R, 4S) stereoisomers of sertraline into sertraline comprises, providing an initial reaction mixture which contains at least one of these stereoisomers, converting the sertraline stereoisomers into an imine form of sertraline. The imine form of sertraline is then reduced so that sertraline and at least one sertraline stereoisomer byproduct is produced in the reaction mixture. The sertraline is then recovered from the reaction mixture, e.g., by fractional crystallization (followed by resolution of sertraline from the cis (1R, 4R) stereoisomer, if necessary). The reaction mixture is then recycled through the same steps so that sertraline is produced from its stereoisomers in an asymptotic yield.

INTERNATIONAL SEARCH REPORT

Int. onal Application No
PCT/IN 01/00001

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C209/88 C07C209/52 C07C211/42 C07B57/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

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[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2001	27/04/2001

Name and mailing address of the ISA	Authorized officer
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